DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group II invention (claims 6, 8, 11, 29 and 30) and election of N-acetylcysteine and SIN-1 as species in the reply filed on 8/11/06 was acknowledged and the traversal arguments were answered in the office action dated 9/11/06.

Applicant's amendment to claims in the response filed on 3/16/09 has been acknowledged.

Claims 6-13, 16-18, 21-25 and 29-31 are pending.

Claims 7, 29 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/11/06.

Claim 18 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/11/06.

Claims 6, 8-13, 16, 17, 21-25 and 31 are examined on the merit.

Any objections and/or rejections made in the previous office action dated 10/14/08 and not specifically discussed here in original or modified form are considered withdrawn.

Withdrawn Rejections

Claim Rejections - 35 USC § 112(1st paragraph-WD)

Applicant's arguments, see page 5, filed 3/16/09, with respect to claims 6, 8-17, 21-25 and 31 have been fully considered and are persuasive. The rejection of claims 6, 8-17, 21-25 and 31 under 35 USC 112, written description has been withdrawn.

Claim Rejections - 35 USC § 102(b)

1. Applicant's arguments, see page 6, filed 3/16/09, with respect to the rejection(s) of claim(s) 6 under 35 USC 102(b) as being anticipated by Buckley have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of applicant's amendments to claim 6.

2. Applicant's arguments, see page 6, filed 3/16/09, with respect to the rejection(s) of claim(s) 6 and 8 under 35 USC 102(b) as being anticipated by Corrales have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of applicant's amendments to claim 6.

3. Applicant's arguments, see pages 7-9, filed 3/16/09, with respect to the rejection(s) of claim(s) 6, 8-17, 21-25 and 31 under 35 USC 103(a) over Corrales in view of Lautt and further in view of Mattia have been fully considered and are persuasive.

Therefore, the rejection has been withdrawn. New ground(s) of rejection is made in view of applicant's amendments to claim 6.

New grounds of rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6 and 8 are rejected under 35 U.S.C. 102(b) as anticipated by Robak, 1995, Pol. J. Pharmacol., 47, 63-67.

In the instant application, applicants claim a pharmaceutical composition comprising:

a) a therapeutically effective amount of hepatic glutathione increasing compound for reducing insulin resistance, wherein the hepatic glutathione increasing compound is at least one of N-acetylcysteine, cysteine esters, cysteine, glutathione, etc., and

b) a therapeutically effective amount of hepatic nitric oxide donor donors for reducing insulin resistance, wherein the hepatic nitric oxide donor is at least one of SIN-1, molsidamine, nitrosylated N-acetylcysteine, etc.

Robak discloses a composition comprising 50 μM Cysteine and 50 μM SIN-1 in 0.02 M phosphate buffer (figure 1, page 65), 50 μM glutathione and 50 μM SIN-1 in 0.02 M phosphate buffer (figure 2, page 65) and 50 μM N-acetylcysteine and 50 μM SIN-1 in

0.02 M phosphate buffer (figure 3, page 66). The disclosure of the afore-mentioned compositions in phosphate buffer reads on the instant pharmaceutical composition of claim 6. The presence of cysteine and glutathione in the composition reads on the instant claim 8 because cysteine and glutathione are known anti-oxidants and Robak discloses that samples without oxygen contained 50 μM cysteine (see description to table 1 on page 64). The instant specification does not define the phrase "therapeutically effective amount" by providing a dosage amount that would constitute a therapeutically an effective amount. The concentration of 50 μM of SIN-1 and 50 μM of N-acetylcysteine reads on the therapeutically effective amounts of instant invention. Since Robak discloses the composition of the SIN-1 (a NO donor) and N-acetylcysteine (a glutathione increasing compound), in an physiological medium it inherently reduces insulin resistance. MPEP section 2112 states that "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer."

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 8 and 11 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kondo, 1997, FEBS Letters, 413, 236-238.

In the instant application, applicants claim a pharmaceutical composition comprising:

a) a therapeutically effective amount of hepatic glutathione increasing compound for reducing insulin resistance, wherein the hepatic glutathione increasing compound is at least one of N-acetylcysteine, cysteine esters, cysteine, glutathione, etc., and

b) a therapeutically effective amount of hepatic nitric oxide donor donors for reducing insulin resistance, wherein the hepatic nitric oxide donor is at least one of SIN-1, molsidamine, nitrosylated N-acetylcysteine, etc.

Kondo discloses that human erythrocytes (10% hematocrit) incubated with 100 μM peroxinitrite in the presence and absence of antioxidants such as 300 μM of glutathione, 300 μM of N-acetylcysteine physiological saline (pH 7.4) (figure 3, page 238). The source of the peroxinitrite has not been expressly disclosed in the detailed description to the figure 3. However, Kondo discloses that 3-morpholinosydnonamine (SIN-1) is known to generate spontaneously both superoxides and nitric oxide concomitantly under physiological conditions and can be used as a convenient source of peroxynitirte (page 237, column 2, paragraph 1). Hence SIN-1 could be the source of the peroxinitrite for the composition disclosed in figure 3. Thus Kondo discloses composition comprising a nitric oxide donor (SIN-1) and N-acetylcysteine in physiological buffer and

hence meets the reads on the instant claims 6 and 8. The instant specification does not define the phrase "therapeutically effective amount" by providing a dosage amount that would constitute a therapeutically an effective amount. The concentration of 100 μM of nitric oxide donor and 300 μM of N-acetyl cysteine reads on the therapeutically effective amounts of instant invention. Human erythrocyte (hematocrit) inherently comprises of serum albumin and hence reads on the instant claim 11 that further requires the presence of albumin.

In this instant case Kondo discloses a composition of a nitric oxide donor (SIN-1) and glutathione increasing compound (glutathione or N-acetylcysteine) in a physiologically acceptable buffer (carrier) and hence meets the limitations of the instant invention. MPEP section 2112 states that "[W]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." Further MPEP states that "[O]nce a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference".

Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 6, 8-10, 12, 13, 16, 17, 21-25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robak, 1995, Pol. J. Pharmacol., 47, 63-67 in view of WO 00/19992 of Lautt and further in view of Mattia, 1998, Diabetologia, 41, 1392-1396.

In the instant application, applicants claim a pharmaceutical composition comprising:

a) a therapeutically effective amount of hepatic glutathione increasing compound for reducing insulin resistance, wherein the hepatic glutathione increasing compound is at least one of N-acetylcysteine, cysteine esters, cysteine, glutathione, etc., and

b) a therapeutically effective amount of hepatic nitric oxide donor donors for reducing insulin resistance, wherein the hepatic nitric oxide donor is at least one of SIN-1, molsidamine, nitrosylated N-acetylcysteine, etc.

Robak discloses a composition comprising 50 μM Cysteine and 50 μM SIN-1 in 0.02 M phosphate buffer (figure 1, page 65), 50 μM glutathione and 50 μM SIN-1 in 0.02

M phosphate buffer (figure 2, page 65) and 50 μM N-acetylcysteine and 50 μM SIN-1 in 0.02 M phosphate buffer (figure 3, page 66). The disclosure of the afore-mentioned compositions in phosphate buffer reads on the instant pharmaceutical composition of claim 6. The presence of cysteine and glutathione in the composition reads on the instant claim 8 because cysteine and glutathione are known anti-oxidants and Robak discloses that samples without oxygen contained 50 μM cysteine (see description to table 1 on page 64). The instant specification does not define the phrase "therapeutically effective amount" by providing a dosage amount that would constitute a therapeutically an effective amount. The concentration of 50 μM of SIN-1 and 50 μM of N-acetylcysteine reads on the therapeutically effective amounts of instant invention. Since Robak discloses the composition of the SIN-1 (a NO donor) and N-acetylcysteine (a glutathione increasing compound), in a physiological medium it inherently reduces insulin resistance.

Robak does not disclose the method of administering the composition of SIN-1 and N-acetylcysteine to reduce insulin resistance in a mammalian patient.

The reference of Lautt discloses composition comprising a nitric oxide donor SIN-1 and a method to increase insulin sensitivity and hence reducing insulin resistance. The composition is administered to treating obesity, insulin resistance and diseases associated with insulin resistance in patients (page 8, lines 3-30). This reads on instant claims 6, 10, 12, 21, 24 and 31. The reference also teaches that the composition can be administered in various ways including oral and intravenous delivery and to humans (page 12, lines 4-23). This reads on instant claims 16, 17 and 25. The reference further teaches that the composition comprises various vehicles, adjuvants and carriers such as liposomes, polymers, antibodies, etc. This reads on instant claim 11. Rapid insulin

sensitivity test (RIST) index is a measure to express insulin sensitivity as the total amount of glucose mg/kg infused over 30 minutes after insulin administration. The reference teaches that RIST after denervation and intraportal SIN-1 significantly reduced the RIST index from 208 mg/kg to 87 mg/kg. Hence administration of SIN-1 improves glucose uptake (page 23, lines 9-15). This reads on instant claim 31.

Mattia, et al., have shown that administration of N-acetylcysteine in non-insulin diabetic patients increases the glutathione and GSH/GSSG ratio concentration in non-insulin dependent diabetic patients (column 2 of 'summary' on page 1392). This reads on instant claims 6, 13 and 24. Since N-acetylcysteine increases the GSH levels, it is an antioxidant and hence reads on instant claims 8 and 23.

It would have been obvious to one of ordinary skill in the art to combine the references of Robak, Lautt and Mattia to arrive at the instant invention. Because, Robak discloses pharmaceutical composition SIN-1 and N-acetylcysteine or glutathione (a glutathione increasing compound), Lautt discloses the composition and method for reducing insulin resistance in a mammal by administration of SIN-1 and the reference of Mattia discloses the composition comprising N-acetyl cysteine to treat non-insulin dependent diabetes. It would have been obvious to one of ordinary skill in the art to use a combination of elected species SIN-1 and a N-acetylcysteine (glutathione increasing compound) in a composition because such a composition has been taught by Robak and each of the two individual species SIN-1 and N-acetylcysteine were taught by Lautt and Mattia to reduce insulin resistance. One would have been motivated to do given the fact Robak teaches the composition in physiologically acceptable medium and Lautt and Mattia have used the individual components of the composition to treat diabetes by

reducing insulin resistance. As set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; the idea of combining them flows logically from their having been individually taught in prior art." In this case SIN-1 and N-acetyl cysteine are used in the composition for reducing the insulin resistance. As afore-described each of these compounds has been known to reduce insulin resistance as taught by Lautt and Mattia. Hence according to *In re Kerkhoven*, the idea of combining two compounds in a composition logically flows as they have been known to posses the property of reducing insulin resistance individually in prior art.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

2. Claims 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over 6,436,996 B1 issued to Vitek, et al.

In the instant application, applicants claim a pharmaceutical composition comprising:

a) a therapeutically effective amount of hepatic glutathione increasing compound for reducing insulin resistance, wherein the hepatic glutathione increasing compound is at least one of N-acetylcysteine, cysteine esters, cysteine, glutathione, etc., and

b) a therapeutically effective amount of hepatic nitric oxide donor donors for reducing insulin resistance, wherein the hepatic nitric oxide donor is at least one of SIN-1, molsidamine, nitrosylated N-acetylcysteine, etc.

Vitek, et al., discloses a method for increasing nitric oxide levels in a subject with the presence of at least one exogenous nitric oxide source selected from the group consisting of SIN-1, N-acetylcysteine, L-arginine, dithiothreitol, cysteine, etc. Although, Vitek, et al., discloses the composition comprising of SIN-1 and N-acetylcysteine (claim 1, column 9, lines 5-8) as an exogenous source of increasing the nitric oxide levels in cells in Alzheimer's patients who suffer from decreased nitric oxide levels associated with the presence of APOE4 alleles, the composition comprises of the species elected in the present invention and hence, when administered, should perform the desired function of glutathione increasing and nitric oxide increasing functions (meeting the limitations of claim 6) in liver. Further, the composition contains the presence of cysteine and dithiothreitol, which are known anti oxidants, and hence meets the limitation of claim 8.

It would have been obvious to one of ordinary skill in the art to use the teachings of Vitek to arrive at the instant invention, because, Vitek discloses a composition comprising at least one of several exogenous nitric oxide donors such as SIN-1, N-acetylcysteine, cysteine, etc. As set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA

1980), "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; the idea of combining them flows logically from their having been individually taught in prior art." In this case SIN-1 and N-acetyl cysteine are used in the composition as exogenous source of nitric oxide. Hence according to *In re Kerkhoven*, the idea of using two compounds having the same property (as nitric oxide donors) in a composition logically flows as they have been known to posses the property of increasing the nitric oxide levels in a subject when administered.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

This application contains claims 7, 18, 29 and 30 drawn to an invention nonelected with traverse in the reply filed on 8/11/06. A complete reply to the final

rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment to claim 6 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
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